

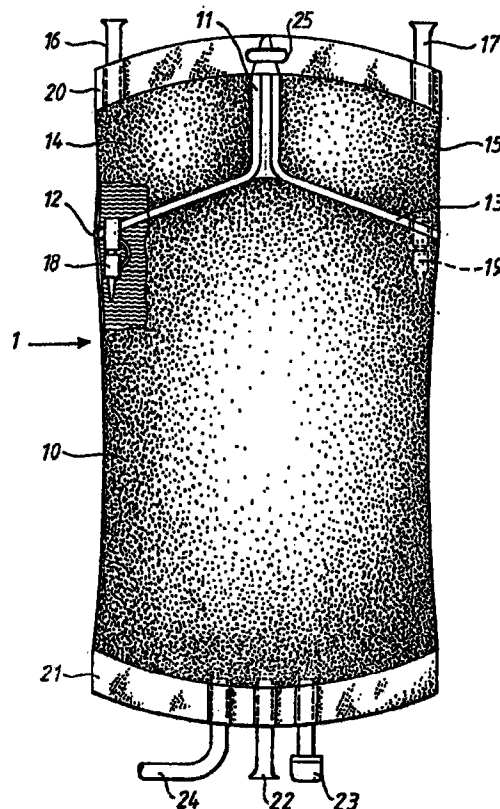


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(21) International Application Number: PCT/SE98/02146 (22) International Filing Date: 27 November 1998 (27.11.98) (30) Priority Data: 9704386-3 28 November 1997 (28.11.97) SE (71) Applicant (for all designated States except US): GAMBRO AB [SE/SE]; Hamngatan 2, P.O. Box 7373, S-103 91 Stockholm (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): WIESLANDER, Anders [SE/SE]; Våpplingevägen 17 A, S-222 38 Lund (SE). RIPPE, Bengt [SE/SE]; Husarvägen 13, S-237 32 Bjärred (SE). (74) Agent: ASKETORP, Göran; Gambro AB, P.O. Box 10101, S-220 10 Lund (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: MULTIPLE COMPARTMENT CONTAINER FOR MEDICAL SOLUTION**(57) Abstract**

Container for medical solution, particularly for peritoneal dialysis. A large compartment (10) contains the majority of the medical solution, such as sodium bicarbonate, sodium lactate and sodium chloride. In addition, a plurality of small compartments (14, 15) are provided which contain partial quantities of the medical solution which are not compatible for long term storage with the contents of the large compartment, such as calcium ions and glucose. By mixing the contents of the first (14) or second (15) of the small compartments with the contents of the large compartment (10), a solution is obtained having 1.5 % or 2.5 % glucose and 1.0 mM or 1.6 mM calcium. By mixing the contents of both the small compartments with the contents of the large compartment, a solution is obtained having 4.0 % glucose and 2.5 mM calcium. Due to the increased ultrafiltration at high glucose concentration, these medical solutions are calcium-neutral during use as peritoneal dialysis solutions.



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5 TITLE

Multiple compartment container for medical solution

10 AREA OF INVENTION

The present invention relates to peritoneal dialysis, where a dialysis solution is present in a multiple compartment container provided with three or more compartments.

15 The invention relates particularly to such a container in which the dialysis solution contains bicarbonate as buffer, as well as glucose and calcium ions.

PRIOR ART

20 A container for peritoneal dialysis is disclosed in WO 97/05852. The container contains conventional dialysis solution with lactate as buffer. The container thus comprises a first large compartment containing sodium lactate, sodium chloride, calcium chloride and magnesium chloride, as well as two small compartments containing glucose of high
25 concentration and low pH. The container is sterilized in an autoclave with the solutions in situ in said compartments. During use, either one or both of the compartments are connected to the large compartment by frangible pins whereby the dialysis solution contains a desired concentration of
30 glucose, such as 1.5%, 2.5% or 4%. Using a three compartment container, it is possible to employ a single container for all three degrees of concentration, which reduces costs for logistics and storage.

35 SUMMARY OF THE INVENTION

An object to the present invention is to adapt the container according to WO 97/05852 for such type of peritoneal dialysis in which the lactate buffer is entirely or partially

exchanged for a buffer consisting of bicarbonate.

As is known, bicarbonate cannot, however, be combined with calcium or magnesium in the large compartment since this may lead to precipitation of, for example, carbonates during long term storage or at high pH. Accordingly, bicarbonate and calcium/magnesium must be separated until shortly before use.

One option would be to include calcium in the small compartments containing glucose and bicarbonate in the large compartment. Glucose and calcium/magnesium are largely compatible, i.e. they do not precipitate. However, the divalent ions catalyse glucose decomposition to a certain extent. During mixing of the contents of the small compartment with the contents of the large compartment shortly before use, the risk of precipitation of carbonates is low since the pH-value of the entire solution is maintained well below pH = 7.4.

A conventional peritoneal dialysis solution has a calcium ion concentration of 1.75 mM (mmol/l) and a magnesium ion concentration between 0.25-0.50 mM. The buffer may be solely bicarbonate which thereby normally exists at a concentration of 30-40 mM or a combination of bicarbonate and lactate, for example 25 mM bicarbonate and 15 mM lactate.

In the following, only calcium ions will be considered since they are of the greatest clinical significance, although the principles of the invention is, of course, equally applicable to magnesium ions.

If the above solution were, however, to be used in a three compartment container of the type which is described in WO 97/05852, a problem arises if the calcium ions are included in the small compartments in one and the same concentration. When the contents of one of the small compartments are mixed with the contents of the large compartment, a concentration of 1.5% glucose and, for example, 1.75 mM calcium is created, which is regulated by the quantity of glucose and the concentration of calcium in the first small compartment. If the contents of the second small compartment are mixed with the contents of the large compartment, a concentration of 2.5% glucose and 1.75 mM calcium results, which is regulated by the

quantity of glucose and the concentration of calcium in the second small compartment. If, however, the third glucose concentration of 4% is to be obtained, the contents of both the first and the second small compartments are mixed with the contents of the large compartment, whereby a glucose concentration of 4% is obtained, but the calcium concentration becomes too great, in this case about 3.5 mM. It therefore does not seem to be possible to provide a three compartment container of this type offering the possibility of three different glucose concentrations, since the calcium concentration will be too high in the presence of the highest glucose concentration. It would be necessary to expand the concept to a four compartment container, which, however, might result in new problems of safety.

A further object of the present invention is to propose a three compartment container of the above-mentioned type in which the above-mentioned problem is solved.

The problematic issues with calcium for peritoneal dialysis, as well as for haemodialysis, are complicated since dialysis patients normally eat calcium carbonate to bind phosphate which is present in food. A portion of the calcium carbonate which is consumed together with food is absorbed in the intestinal tract and increases the calcium concentration in the blood. At the same time, the calcium carbonate binds phosphate so that the phosphate load on the patient is reduced. Phosphate is a molecule which is difficult to remove from the body via dialysis since it does not pass easily through membranes, whether they be synthetic membranes or peritoneal membranes.

The calcium concentration in the peritoneal dialysis solution which is generally recommended today is 1.75 mM. This would seem to be a suitable compromise which corresponds to the normal physiological concentration of free calcium in blood, since calcium is present in blood both freely as well as bound to protein, particularly albumin. If the calcium concentration in the patient is increased, a removal of calcium takes place, whereas if the concentration is too low, calcium is supplied to the body.

Should a surplus of calcium arise, hypercalciemia, the following symptoms, among others, result: vomiting, dizziness, reduced muscle function, ECG-disorders and necrosis calcification.

5 Hypercalciemia is usually rectified by the patient avoiding consumption of calcium carbonate for several days, whereupon the calcium concentration quickly reduces.

On the other hand, hypocalciemia results in i.a. the following symptoms: cramps, hyper-reflexes, spasms, ECG-changes and hyperparathyroidism.

10 Hypocalciemia is normally counteracted by increased intake of calcium carbonate, while the calcium concentration in the dialysis solution is normally kept constant.

It is recognized that the problematics with calcium are difficult since the above-mentioned symptoms are difficult to diagnose.

15 More recently, it has been proposed to further reduce the calcium concentration in dialysis solution to 1.35, 1.25 or even 1.0 mM. The reason is that the oral intake of calcium carbonate can thereby be increased and further reduce the phosphate charge on the patient. The risk for hypocalciemia increases therewith and increased awareness for diagnosis and treatment is necessary.

20 Earlier trials have shown that the transport of calcium ions across the peritoneal membrane is affected by the glucose concentration in the peritoneal dialysis solution. This effect is, however, rarely discussed.

25 According to the present invention, however, this discovery is used to solve the above-mentioned problem in a three compartment container of the type which is described in WO 97/05852 to thereby adapt this container to a buffer comprising bicarbonate.

30 Our experiments with simulations of calcium transport across the peritoneal membrane indicate the following unexpected results. If a peritoneal dialysis solution is to be neutral (in- and outflow the same) with regard to the calcium transport during a four hour period, it should comprise about 35 1.2 mM calcium at 1.5% glucose, about 1.6 mM at 2.5% glucose

and, finally, about 2.3 mM calcium at 4.0% glucose, i.e. the calcium concentration should be substantially proportional to the glucose concentration in the final solution.

This can be achieved in a three compartment container by means of calcium being present in substantially the same concentration in the two small glucose compartments. The final glucose concentration in the mixed solution is determined by the volume of the small compartments since the glucose concentration is identical in the small glucose compartments, for example 50%. This results in that the calcium concentration will always remain proportional to the glucose concentration. The higher the glucose concentration (greater volume), the more ultrafiltration and thus also higher calcium concentration in the mixed solution. The calcium concentration may in that respect be selected so that the patient either has a net loss, net gain or neutral calcium balance irrespective of the ultra- filtration and the glucose concentration.

A further object in the present invention is to provide a three compartment container of the above-mentioned type with bicarbonate in the large compartment and glucose together with calcium in the two small compartments, whereby the increase in the calcium concentration at the highest glucose concentration results in better calcium control than previously. This invention is completely different from previously known methods in which the same calcium concentration has always been used irrespective of the glucose concentration.

By using a peritoneal dialysis solution in which the calcium concentration is proportional to the glucose concentration, it is possible to use one and the same solution in the small compartments, i.e. the equipment which is used to fill the three compartment container need only produce solutions having two different compositions, one for the large compartment and one for the two small compartments. In this manner, the manufacturing costs are reduced.

Thus, there is provided according to the invention a container containing a medical solution, particularly for peritoneal dialysis, consisting of a large compartment having a volume which is sufficiently large to contain the finally

prepared medical solution, and at least two small compartments which contain partial quantities of the medical solution which are incompatible for long term storage with the contents of the large compartment. The large compartment comprises bicarbonate ions and the small compartments comprises glucose and calcium ions.

According to the invention, it is an advantage if the glucose concentration is substantially proportional to the calcium ion concentration in the finally prepared medical solution.

To obtain such proportional concentration, the two small compartments may comprises solutions having the same concentration of glucose and calcium, though having different volumes, or the first of the small compartments contains glucose and calcium ions with such a concentration that the glucose concentration when mixing the contents of said first small compartment with the contents of the large compartment obtains a first predetermined value, such as 1.5%, and the calcium ion concentration obtains a second predetermined value, such as 1.0 mM, while the second of the small compartments contains glucose and calcium ions having such a concentration so that the glucose concentration in the finally prepared solution when mixing the contents of said second small compartment with the contents of the large compartment obtains a third predetermined value, such as 2.5%, and the calcium ion concentration obtains a fourth predetermined value, such as 1.6 mM, and finally the contents of the first and the second of the small compartments may be mixed with the contents of the large compartment to obtain a finally prepared solution with higher concentrations of glucose and calcium ions, such as 4% glucose concentration and 2.5 mM calcium.

The small compartments may further comprise magnesium ions, for example in a concentration such that the resulting concentration in the finally prepared medical solution is about 0.25-0.75 mM.

The invention also relates to a method for preparing a medical solution, particularly for peritoneal dialysis, in a container consisting of a first large compartment having a

volume which is sufficiently large to contain the finally prepared medical solution, and a plurality of small compartments which contain partial quantities of the medical solution which are not compatible for long term storage with the contents of the large compartment. The large compartment comprises bicarbonate ions and the small compartments comprise glucose and calcium ions. The contents of one or more of the small compartments are mixed with the contents of the large compartment to produce a medical solution in which the concentration of glucose is substantially proportional to the concentration of calcium ions.

Finally, the invention also relates to a use of a container for preparation of a peritoneal dialysis solution in which the concentrations of glucose and calcium ions are substantially proportional.

BRIEF DESCRIPTION OF THE DRAWINGS

Further objects, problems, solutions and features will be apparent from the following detailed description of the invention with reference to the drawings describing several embodiments of the invention.

Fig. 1 is a plan view of a container which may be used in the present invention.

Figs. 2, 3 and 4 are computer-simulated diagrams which show the calcium balance across the peritoneal membrane.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Fig. 1 discloses a three compartment container which may be used in the present invention. The container 1 is of the type which is sealed at both ends with weld seams 20 and 21. The container is divided into a large compartment 10 and two small compartments 14 and 15 by weld seams 11, 12 and 13.

The small compartment 14 and/or 15 may communicate with the large compartment 10 by means of frangible pins 18, 19 which are normally sealed but can be manually opened. When the frangible pin 18 and/or 19 is opened, the contents in the compartments 14 and/or 15 flow down into the large compartment 10 and mix with the contents therein.

During manufacture of the container, suitable solution is supplied to the various compartments 10, 14 and 15 via inlet tubes 16, 17 and 22 extending through the weld seams 20 and 21. A sample and/or infusion port 23 extending through the weld seam 21 permits sampling from, and infusion to, the compartment 10.

The solution in the compartment 10 is supplied to a patient via a conduit 24. The container is placed on a stand by means of an opening 25 in the upper weld seam 20. The bag described so far is substantially identical to the one disclosed in WO 97/05852.

The container preferably has a size such that two litres of peritoneal dialysis solution are accommodated in the large compartment 10 in a ready-mixed state. Larger or smaller containers are of course feasible according to the invention.

We have studied the transport of calcium ions across the peritoneal membrane as a function of time, during treatment with a peritoneal dialysis solution comprising glucose as well as different concentrations of calcium ions. Figs. 2, 3 and 4 show the results for glucose concentrations of 1.5%, 2.5% and 4%, respectively. It is apparent that the calcium transport is not only dependent on the concentration gradient across the peritoneal membrane, but also ultrafiltration contributes. A normal CAPD-treatment requires that the patient carries a PD-solution for four hours (240 minutes) and then exchanges it for a fresh PD-solution. If such a PD-solution should result in zero transport of calcium across the peritoneal membrane during the 240 minute period, calcium concentrations of 1.2 mM, 1.6 mM and 2.3 mM respectively are required.

The calculations presuppose certain properties of i.a. the peritoneal membrane. We have concluded that a calcium concentration which is substantially proportional to the glucose concentration results in a substantially calcium-neutral treatment, i.e. the calcium transport across the peritoneal membrane will be substantially the same, independent of the selected glucose concentration.

In accordance with the present invention, the container 1 is to be used to prepare a peritoneal dialysis solution in

which the buffer consists of bicarbonate. Accordingly, the solutions in the various compartments may be the following.

EXAMPLE 1

5 The compartment 10 contains 1900 ml with the composition:

sodium bicarbonate	40 mM
sodium chloride	132 mM

10 Compartment 14 contains 100 ml of the composition:

glucose	30%
calcium chloride	20 mM
magnesium chloride	5 mM
15 sodium chloride	132 mM

Compartment 15 contains 100 ml of the composition:

glucose	50%
20 calcium chloride	33 mM
magnesium chloride	8 mM
sodium chloride	132 mM

By mixing the contents of compartment 14 and compartment
25 10, a peritoneal dialysis solution is obtained with the following composition:

glucose	1.5%
calcium	1.0 mM
30 bicarbonate	38 mM
sodium	132 mM
magnesium	0.25 mM

Mixing the contents of compartment 15 and compartment 10
35 results in a dialysis solution having the composition:

	glucose	2.5%
	calcium	1.65 mM
	bicarbonate	38 mM
	sodium	132 mM
5	magnesium	0.4 mM

By mixing the contents of both compartments 14 and 15 with the contents of compartment 10, a dialysis solution is obtained having the following composition:

10

	glucose	4.0%
	calcium	2.5 mM
	bicarbonate	36 mM
	sodium	132 mM
15	magnesium	0.6 mM

In a second example of the invention, the contents of each of the small compartments have the same composition according to the following:

20

EXAMPLE 2

Compartment 10 contains 1950 ml of the composition:

	sodium bicarbonate	25 mM
25	sodium lactate	15 mM
	sodium chloride	132 mM

Compartment 14 contains 60 ml of the composition:

30	glucose	50%
	calcium chloride	33 mM
	magnesium chloride	8 mM
	sodium chloride	132 mM

Compartment 15 contains 100 ml of the composition:

glucose	50%
calcium chloride	33 mM
5 magnesium chloride	8 mM
sodium chloride	132 mM

10 In a further alternative embodiment of the present invention, solutions are employed with the following compositions in the various compartments 10, 14 and 15.

EXAMPLE 3

Compartment 10 contains 1850 ml of the composition:

15 sodium bicarbonate	27 mM
sodium lactate	16 mM
sodium chloride	132 mM

Compartment 14 contains 150 ml of the composition:

20 glucose	20%
calcium chloride	13 mM
magnesium chloride	3.2 mM
sodium chloride	132 mM

25 Compartment 15 contains 260 ml of the composition:

glucose	20%
calcium chloride	12.5 mM
30 magnesium chloride	3.1 mM
sodium chloride	132 mM

35 Because of the effect of dilution, the calcium concentration will be somewhat lower than in the first two examples.

To avoid problems with high pH-values, the pH-value in the large compartment is normally adjusted to a pH = 7.2. The pH-value in the small compartments is normally low, about 3.0, in

order to prevent glucose decomposition during autoclaving.

When a patient uses a container according to the present invention, he will experience a calcium inflow or outflow which is determined by the concentration of free calcium in the blood and the concentration of calcium in the finally prepared dialysis solution as well as the glucose concentration. In the case with the highest glucose concentration, the net effect will be approximately the same as with the two lower concentrations and the use of the container according to the invention is, therefore, easy and simple for the patient.

The invention has been described above with reference to preferred embodiments of the invention. A skilled person will recognize that further combinations are possible. Modifications which are apparent to a skilled person are intended to be incorporated within the scope of the invention. The invention is limited only by the appended claims.

5 CLAIMS

1. Container containing a medical solution, particularly for peritoneal dialysis, consisting of a large compartment (10) having a volume which is sufficiently large to contain the finally prepared medical solution, and at least two small compartments (14, 15) which contain partial quantities of the medical solution which are incompatible for long term storage with the contents of the large compartment, **characterized** in that the large compartment (10) comprises bicarbonate ions and the small compartments (14, 15) comprises glucose and calcium ions.

2. Container according to claim 1, **characterized** in that the glucose concentration is substantially proportional to the calcium ion concentration in the finally prepared medical solution.

3. Container according to claim 2, **characterized** in that the small compartments (14, 15) comprises solutions having the same concentration of glucose and calcium, though having different volumes.

4. Container according to claim 1, **characterized** in that a first (14) of the small compartments contains glucose and calcium ions with such a concentration that the glucose concentration when mixing the contents of said first small compartment with the contents of the large compartment obtains a first predetermined value, such as 1.5%, and the calcium ion concentration obtains a second predetermined value, such as 1.0 mM,

a second (15) of the small compartments contains glucose and calcium ions having such a concentration that the glucose concentration in the finally prepared solution when mixing the contents of said second small compartment with the contents of the large compartment obtains a third predetermined value, such as 2.5%, and the calcium ion concentration obtains a fourth predetermined value, such as 1.6 mM,

and the contents of the first (14) and the second (15) of the small compartments may be mixed with the contents of the large compartment (10) to obtain a finally prepared solution with higher concentrations of glucose and calcium ions, such as 4% glucose concentration and 2.5 mM calcium.

5 5. Container according to any one of the preceding claims, **characterized** in that the small compartments (14, 15) further comprises magnesium ions, for example in a concentration such that the resulting concentration in the finally prepared
10 medical solution is about 0.25-0.75 mM.

6. Method for preparing a medical solution, particularly for peritoneal dialysis, in a container consisting of a first large compartment having a volume which is sufficiently large to contain the finally prepared medical solution, and a
15 plurality of small compartments which contain partial quantities of the medical solution which are not compatible for long term storage with the contents of the large compartment, **characterized** in that the large compartment comprises bicarbonate ions and the small compartments comprise
20 glucose and calcium ions, and in that the contents of one or more of the small compartments are mixed with the contents of the large compartment to produce a medical solution in which the concentration of glucose is substantially proportional to the concentration of calcium ions.

25 7. Use of a container according to any one of claims 1-5 for preparation of a peritoneal dialysis solution in which the concentrations of glucose and calcium ions are substantially proportional.

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Fig.1

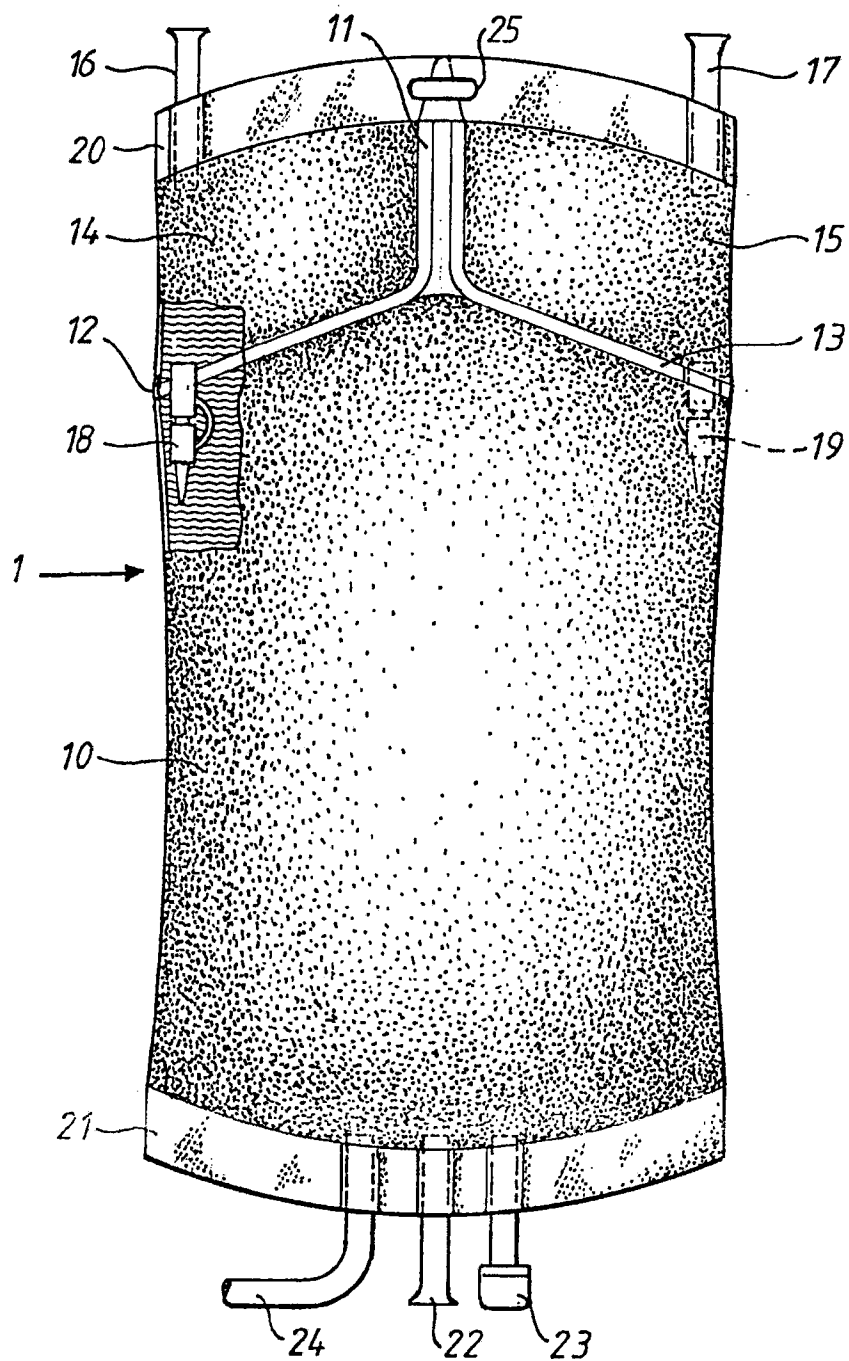


Fig.2

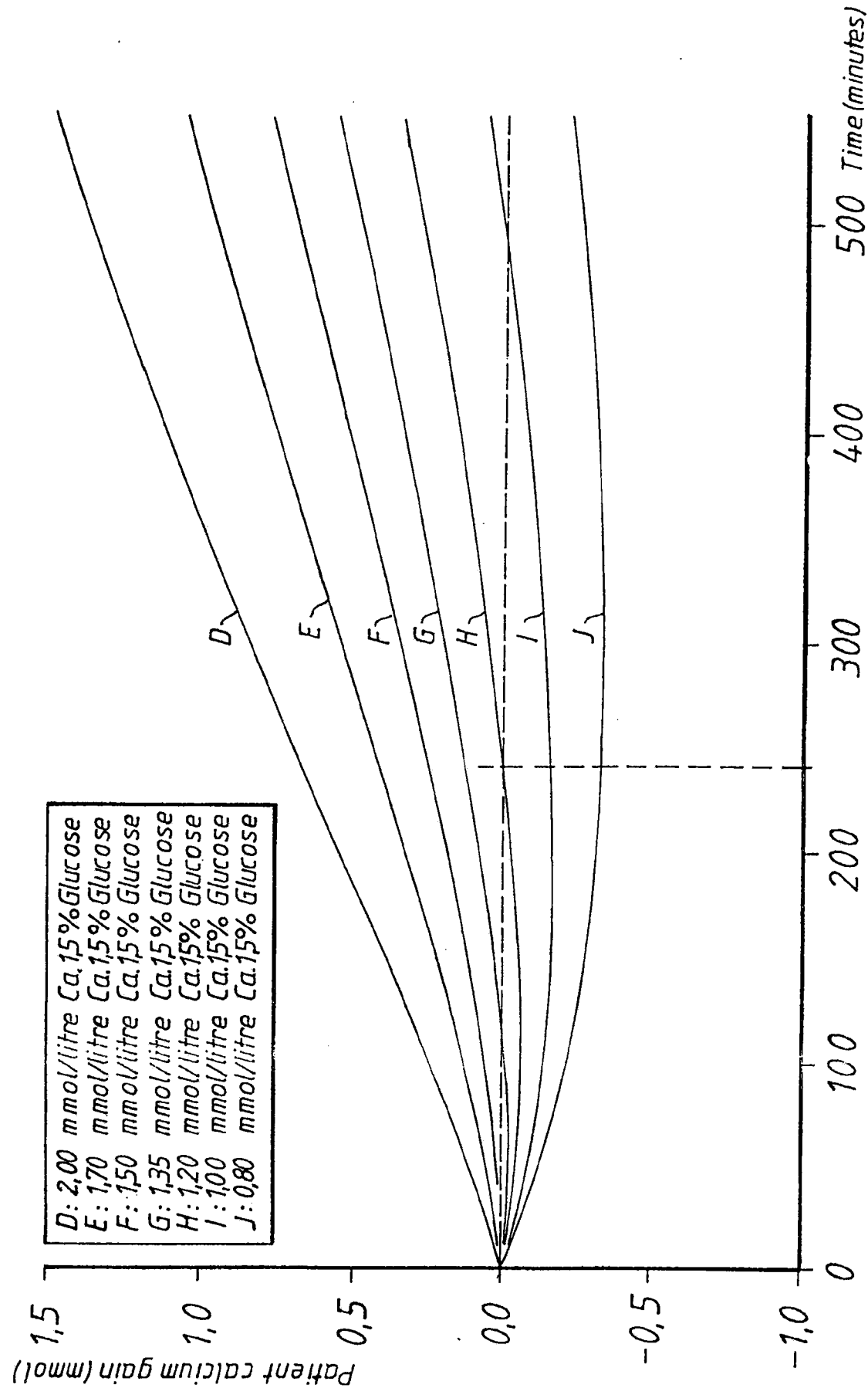


Fig.3

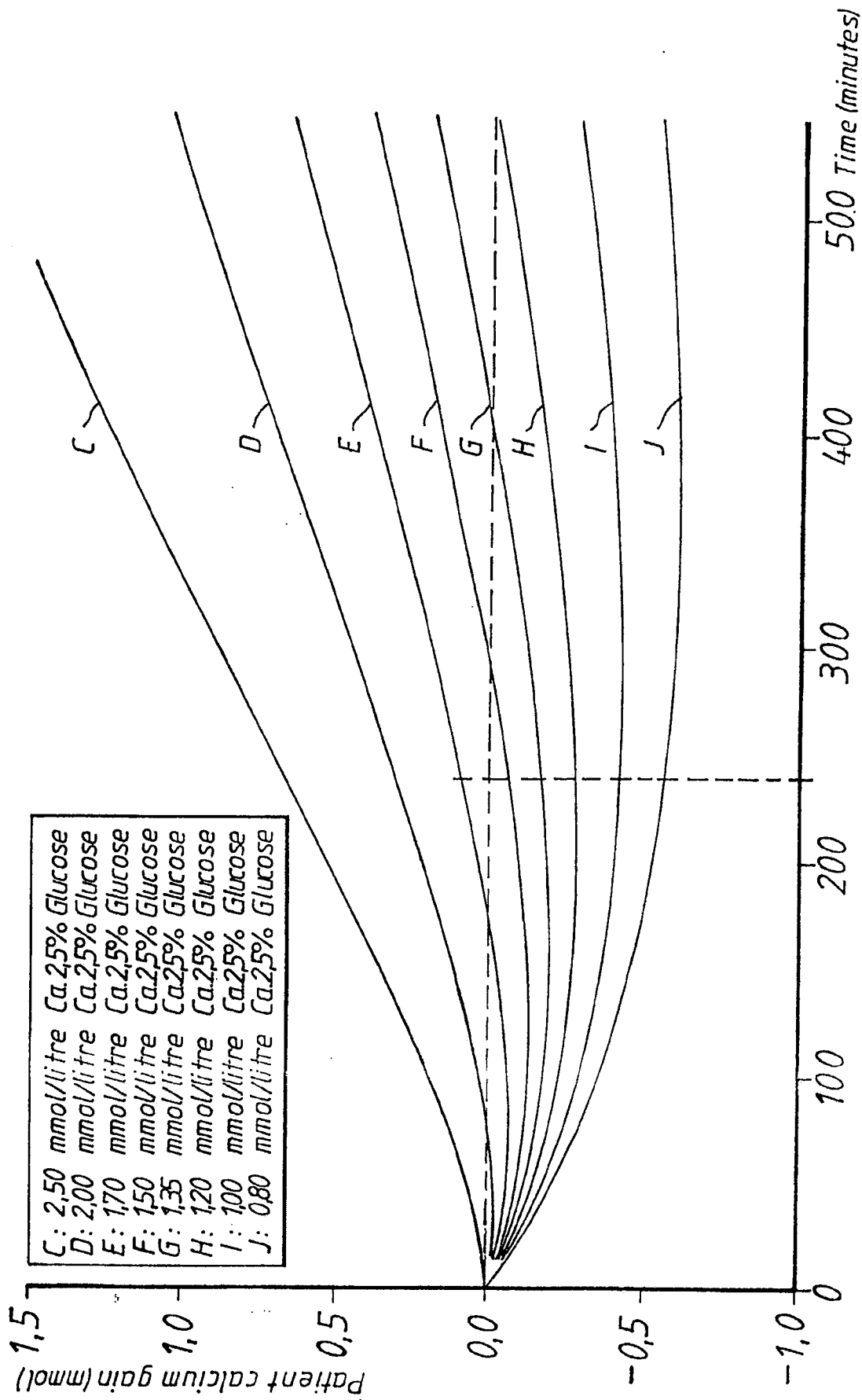
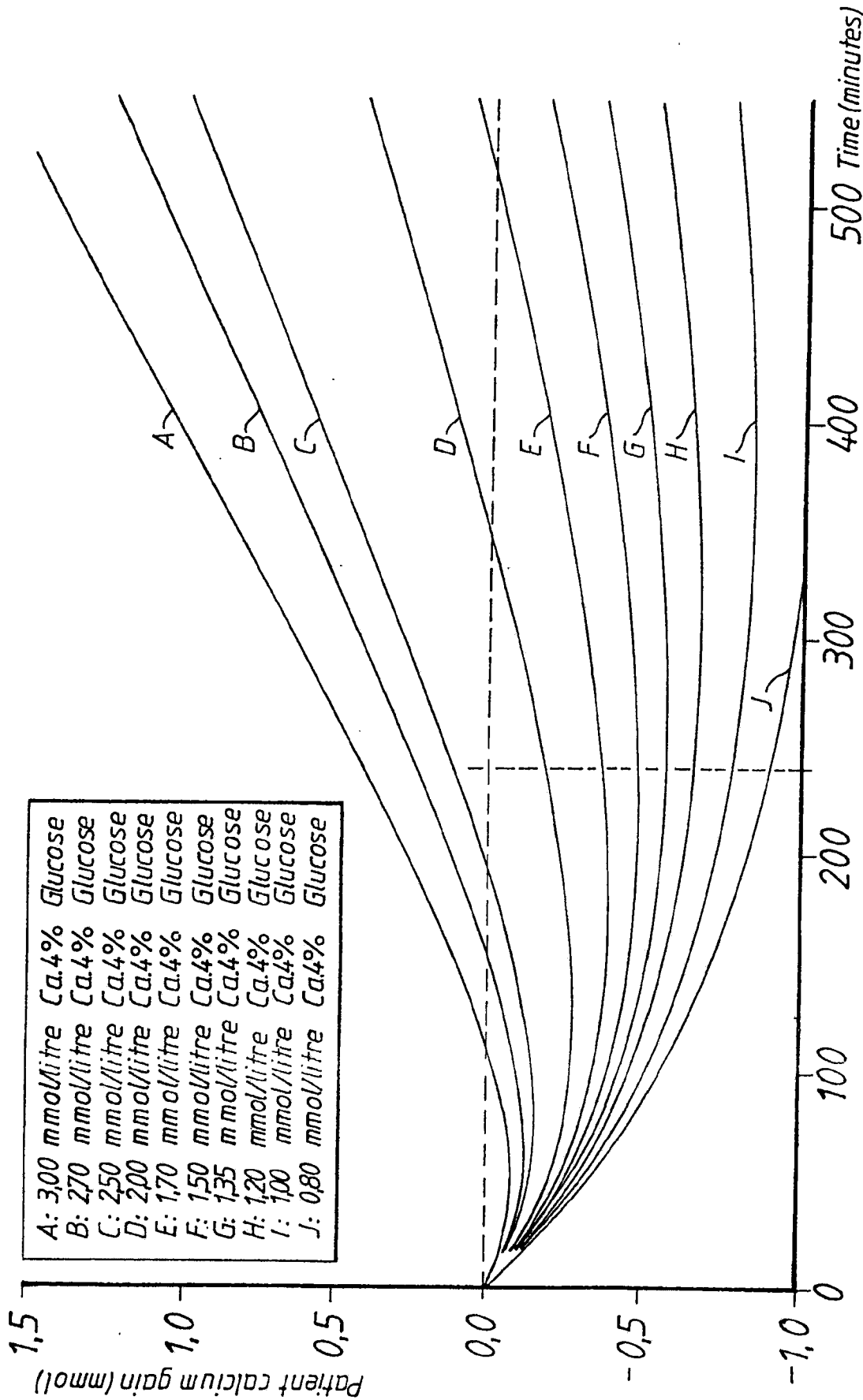


Fig.4



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02146

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61J 1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0295204 A1 (VIFORS S.A.), 24 May 1998 (24.05.98), figures 1-2, claims 1-7 ---	1-3,5-6
X	EP 0442406 A1 (MATERIAL ENGINEERING TECHNOLOGY LABARATORY.INC.), 24 May 1988 (24.05.88), figure 14, claims 1-15 --	1-3,5-6
X	SE 9704386-3 A (GAMBRO AB), 8 February 1997 (08.02.97), figure 4, claims 1-10 -- -----	1-3,5-6

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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INTERNATIONAL SEARCH REPORT
Information on patent family members

02/03/99

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0295204 A1	24/05/98	SE 0295204 T3 CH 686778 A JP 7106755 B JP 63317481 A US 4997083 A	28/06/96 15/11/95 26/12/88 05/03/91
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